REMARKS

The Office Action

Claims 92, 129, and 132-136 are pending and under examination. Claim 92 is rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. Claim 136 is rejected under 35 U.S.C. § 112, first paragraph, for reciting new matter. All examined claims are rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed in detail below.

Amendments to the Claims

Claims 132 and 135 have been amended. The claims have been amended to recite 90% sequence identity to SEQ ID NO: 4. Support for the amendments is found throughout the specification as filed, for example, at page 22, lines 20-24; at page 24, lines 11-14; and at page 32, lines 4-8.

New claims 137-143 have been added. New claim 137, which depends from claim 92, specifies that any change to an amino acid marked in Figure 3a as fully conserved is a conservative substitution. Support for the amendment is found throughout the specification, for example, at page 21, lines 12-14 and at page 22, lines 7-9.

New claim 138, which depends from claim 92, recites 98% sequence identity to SEQ ID NO: 4. Support for the amendment finds basis, for example, at page 22, lines 20-25; at page 24, lines 11-15; and at page 32, lines 4-9.

New claim 139 relates to a therapeutic use of a polypeptide with at least 95% sequence identity to, and all conserved cysteines of, SEQ ID NO: 4. Furthermore, the polypeptide comprises AA_{30}-AA_{288} of SEQ ID NO: 3 or a variant thereof with less than 5 changed amino acids. AA_{30}-AA_{288} of SEQ ID NO: 3 is identical to AA_{7}-AA_{265} of SEQ ID NO: 4 and is thus a fragment of SEQ ID NO: 4. Support for the amendment can be found, for example, at page 19, lines 32-33 and at page 20, lines 4-7.

New claim 140, which depends from claim 139, specifies that 1 or 2 amino acids have been changed relative to the fragment of SEQ ID NO: 3. This finds support, for example, at page 20, lines 6-7.

New claim 141, which depends from claim 135, recites 95% sequence identity to SEQ ID NO: 4. This finds basis, for example, at page 22, lines 20-25; at page 24, lines 11-14; and at page 32, lines 4-9.

New claim 142 relates to a therapeutic use of a polypeptide with at least 95% sequence identity to, and all conserved cysteines of, SEQ ID NO 4, and in which any substitution to a residue marked in Figure 3a as fully conserved (*) is a conservative substitution. Support for this amendment can be found, for example, at page 21, lines 12-14 and at page 22, lines 7-9.

New claim 143, which depends from claim 142, recites what is meant by a conservative substitution. Support for this amendment can be found, for example, at page 21, lines 16-18.

No new matter has been added by the present amendments.

Rejection under 35 U.S.C. § 112, First Paragraph – Written Description

Claim 92 stands rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In setting forth the rejection, the Office states that "base claim 95 [sic] does not recite what critical amino acid residues must be present in order to reasonably show a correlation between structure and function. Therefore, base claim 92 remains rejected for the reasons previously made of record; analogous to the situation decided in Fiers v. Revel, and Univ. California v. Eli Lilly and Co." (Office action, page 3). For the reasons set forth below, Applicants request that the rejection be reconsidered and withdrawn.

The written description standard

In response, Applicants first note that the initial burden for supporting a written description rejection is on the Office. "A description as filed is presumed to be adequate, unless and until sufficient evidence or reasoning to the contrary has been presented by the examiner to

rebut the presumption." (M.P.E.P. § 2163(III)(A)). Under this burden, the Office "must set forth express findings of fact...which support the lack of written description conclusion." (Id.) A *prima facie* rejection requires the Office to provide "reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed." (Id.)

As set forth in M.P.E.P. § 2163(II)(A)(3)(a):

> "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. >See also *Capon v. Eshhar*, 418 F.3d 1349,1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005) ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution."). < If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met."

Applicants submit that the Office has not adequately supported the rejection so as to shift the burden to Applicants to further demonstrate possession.

Case law cited by the Office

The Office cites two decisions in support of the rejection. However, both decisions support the Applicant's position that the specification provides adequate written description.

The Court of Appeals for the Federal Circuit in *Fiers v. Revel* concluded:

> "An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. Revel's specification does not do that. Revel's application does not even demonstrate that the disclosed method actually leads to the DNA, and thus that he had possession of the invention, since it only discloses a clone that might be used to obtain mRNA coding for J-IF.11 A bare reference to a DNA with a statement that it can be obtained by reverse

> transcription is not a description; it does not indicate that Revel was in possession of the DNA. Revel's argument that correspondence between the language of the count and language in the specification is sufficient to satisfy the written description requirement is unpersuasive when none of that language particularly describes the DNA."

Fiers v. Revel, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993). The Court further asserted:

> "We conclude that Sugano is entitled to rely on his disclosure as enabling since it sets forth a detailed teaching of a method for obtaining a DNA coding for J-IF and the Board did not err in determining that Fiers presented no convincing evidence impeaching the truth of the statements in Sugano's patent specification. We also conclude that *Sugano's application satisfies the written description requirement since it sets forth the complete and correct nucleotide sequence of a DNA* coding for J-IF and thus "convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, [Sugano] was in possession of the [DNA coding for J-IF]." See *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1117. The Board correctly determined that Sugano's March 19, 1980 Japanese application satisfies the requirements of section 112, first paragraph, and that Sugano thus met his burden to establish entitlement to that filing date." (Emphasis added.)

Id. at 1172. The Court, in *Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), came to a similar conclusion, namely that in order to satisfy the written description requirement a description of the cDNA is required.

The conclusion that can be drawn from *Fiers v. Ravel* and *Univ. of Cal. v. Eli Lilly & Co.* is that there is adequate written description if the complete and correct DNA sequence is disclosed. Applied to the facts of the present case, the person of skill in the art would conclude that the present application does contain a written description because the reference polypeptide sequence is described along with a recitation of preferred and non-preferred positions for mutagenesis. Thus, the evidence as a whole demonstrates that Applicants were in possession of both the NsG33 polypeptides recited in claim 92 and the methods of using them for treating the Huntington's disease.

Acknowledgement by the Office

The Office acknowledges that the specification describes "what amino acids are not to be mutated (i.e., conserved) to meet the limitation of 'at least 95% sequence identity...'." (Office action, page 3). Claim 92 does not recite what critical amino acid residues must be present in order to reasonably show a correlation between structure and function, and the claim does not need to recite such structure-function relationship. According to 35 U.S.C. § 112, the *specification* shall contain a written description of the invention. (Emphasis added). As acknowledged by the Office, the specification does recite which critical amino acid residues can and cannot be mutated as well as which residues should only be subject to conservative substitutions. The written description requirement is therefore met with respect to claim 92.

Disclosure in the specification

Viewing the application as a whole, the person of skill in the art would realize that the Applicants were in possession of the NsG33 proteins recited in the claims and the claimed methods overall. The claimed methods provide that the NsG33 protein administered comprises an amino acid sequence with 95% identity to a clearly defined structure, SEQ ID NO: 4, which was shown in the application to correspond to a neurotrophic protein. Based on the length of SEQ ID NO: 4 (270 amino acids) the proteins recited in the claims will vary from this reference sequence by up to 13-14 amino acids. In view of this high level of structural similarity to the reference sequence, the person of skill in the art would a priori expect most variants to retain the neurotrophic activity of SEQ ID NO: 4.

The application further directs the skilled reader to the conserved amino acids shared by NsG33 proteins from different organisms, as illustrated in the sequence alignment in Figure 3. The skilled reader would understand that the conserved motifs defined by the fully conserved residues are likely to be important to the recited proteins' function and that any non-conservative

deviations from the sequence of SEQ ID NO: 4 should therefore likely be made outside of these conserved residues/motifs.

The specification identifies in the alignment of Figure 3 extensive motifs/domains constituting approximately 80% of the amino acids of SEQ ID NO: 4 that are responsible for the biological (neurotrophic) activity (page 26, lines 28-36). The specification also predicts that conservative mutations in these conserved motifs/domains will result in a protein having neurotrophic activity (page 22, lines 7-9). Although all conservative amino acid substitutions in these domains will not necessarily result in a protein having neurotrophic activity, those of ordinary skill in the art would expect that many of these conservative substitutions would result in a protein having the required neurotrophic activity. Further, amino acid substitutions outside of the fully conserved motifs/domains are unlikely to greatly affect the neurotrophic activity. Thus, any change to an amino acid which is unconserved, weakly conserved, or strongly conserved in the alignment of Figure 3a is preferred (page 6, lines 11-12). Therefore, a correlation exists between the function of the claimed protein and the structure of the conserved motifs/domains.

The comparison of human, mouse, and rat NsG33 in Figure 3 provides the person of skill in the art with a very powerful structure-function understanding of the recited proteins. In view of the structural differences between the different NsG33 polypeptides and the fact that these polypeptides nevertheless possess neurotrophic properties, proteins comprising an amino acid sequence at least 95% identical to SEQ ID NO: 4 would be expected to be functional, and the skilled reader would conclude that the Applicants were in possession of the claimed methods.

In fact, the *Written Description Training Materials* (Revision 1, March 25, 2008) ("the Materials") support this analysis. Applicants submit that in following the guidelines of the Materials, the skilled reader would conclude that the claims are adequately described. Specifically, Example 11B of the Materials analyzes claims to nucleic acids encoding proteins with 85% identity to a reference sequence and which retains a particular function: "novel activity Y" (the Materials, pages 39-40). No variants of the reference sequences are described in the referenced hypothetical specification, and the reference sequence "does not share significant sequence identity with any

known polypeptide or polypeptide family" (*Id.*, page 40). Furthermore, the hypothetical specification "fails to teach which of the nucleic acid sequences that encode a polypeptide with at least 85% sequence identity to SEQ ID NO: 2 encode a polypeptide having the required activity Y" (*Id.*, page 41).

Nevertheless, the Materials conclude that the claim is adequately supported based on the identification of two domains in the protein believed (but not demonstrated) to be important for the protein's function. The guidelines reason that, following well-accepted knowledge in the art:

> "Conservative mutations in these [two] domains (e.g., one basic amino acid substituted for another basic amino acid) will still result in a protein having activity Y, whereas most non-conservative mutations in these domains will not result in a polypeptide having the recited activity ... [and] that most mutations, conservative or non-conservative, outside the two domains will not affect activity Y to any great extent." (*Id.*, page 40).

If the claims in Example 11B of the Materials are adequately described then there should be no question that Applicants' claims are adequately described. First, Applicants' claims recite a more stringent structural limitation than the claims of Example 11B, a 95% versus 85% sequence identity, respectively. In addition, whereas the specification analysed in Example 11B of the Materials describes a protein with no significant sequence identity to known proteins, the NsG33 proteins in the current claims have orthologues from several species and constitute a family of growth factors together with another protein as illustrated in the alignment of Figure 5. With the sequence alignments provided in the specification and the identification of the conserved cysteine residues in the alignments and in the specification, the skilled reader would recognize a much more powerful structure-function correlation than what was considered adequate in Example 11B of the Materials. Where the specification in Example 11B does not describe particular functional variants and merely identifies two domains believed to be important for function, the current claims allow the skilled reader to develop a higher resolution description of sequence variants of SEQ ID NO: 4 that are likely to retain neurotrophic function.

Thus, following the instructions by the Courts, MPEP and the Materials, the skilled reader would conclude that Applicants were in possession of the polypeptides recited in claim 92 and the claimed methods of use. This rejection should be withdrawn.

Even if the Office does not agree as to the amended claims, Applicants have included new claims for the Office's consideration. New claim 137 provides that any amino acid substitution to SEQ ID NO: 4 is a conservative substitution. Even assuming that the entire structure of SEQ ID NO: 4 is a domain required for function (analogous to the two domains in Example 11B), the Materials expressly endorse the conclusion that conservative substitutions within a domain believed to be important for function should retain protein function (see Materials, page 40). For these additional reasons, this new claim is also adequately described.

New claim 138 recites 98% sequence identity to SEQ ID NO: 4 and is thus a narrower claim than claim 92. With up to 2% amino acid changes, the claim allows 5-6 amino acid changes to the 270 amino acids of SEQ ID NO: 4.

New claim 139 provides a structure-function relationship by requiring that the neurotrophic polypeptides have at least 95% sequence identity to SEQ ID NO: 4, possess the conserved cysteines, and comprise less than five changes to the core sequence (from the first to the last conserved cysteine residue in SEQ ID NO: 4). The specification, at page 20, lines 4-8, describes the fragment, recited at page 19, lines 32-33, as the core fragment. The person of skill in the art knows that the core sequence of a growth factor with a conserved cysteine pattern is the core sequence important for maintaining bioactivity, in this case neurotrophic activity. The core sequence with the spacing between the conserved cysteine residues defines the three-dimensional structure of the neurotrophic proteins, while the C- and N- terminal regions have limited, if any, effect on the three-dimensional structure. The core sequence is 259 amino acids long. According to claim 139, less than five of these amino acid residues, but none of the conserved cysteine residues, can be changed. Although all amino acid substitutions in the core sequence will not necessarily result in a protein having neurotrophic activity, those of ordinary skill in the art would expect that many of these substitutions would result in a protein having the required neurotrophic activity, in

particular if the substitutions are conservative as taught by the specification. Further, amino acid substitutions outside of the fully conserved domains are unlikely to greatly affect the neurotrophic activity. Claim 139 therefore fulfils the written description requirement.

New claim 142 provides a structure-function relationship by requiring that the neurotrophic polypeptides have at least 95% sequence identity to SEQ ID NO 4, possess the conserved cysteines, and comprise only conservative substitutions, if any substitutions are made, to the residues identified as fully conserved in the alignment of Figure 3a. The claim identifies the conserved residues, which constitute approximately 80% of SEQ ID NO: 4 as residues important for the neurotropic function. The claim requires that any substitution to these amino acids must be conservative, as specified at page 22, lines 7-9. The notion that conservative substitutions to amino acids identified as a domain/motif is specifically endorsed by the Materials, for example, at Example 11B, page 40. Although all amino acid substitutions among the conserved residues will not necessarily result in a protein having neurotrophic activity, those of ordinary skill in the art would expect that many of the conservative substitutions would result in a protein having the required neurotrophic activity. Further, amino acid substitutions outside of the fully conserved domains are unlikely to greatly affect the neurotrophic activity.

New claim 143 limits claim 142 further by specifying what is meant by a conservative substitution.

Rejection under 35 U.S.C. § 112, First Paragraph – New Matter

Claim 136 stands rejected under 35 U.S.C. § 112, first paragraph, for new matter. The Office asserts that "[n]o proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant application is apparent in 'Example 15' for the recitation of 'capable of protecting striatal neurons against degeneration'; thereby, constituting new matter" (Office action, page 4). Without assenting to the rejection, Applicants have cancelled claim 136, thereby rendering the rejection moot.

Rejections under 35 U.S.C. § 103(a)

Claims 92, 129, and 132-136 stand rejected under 35 U.S.C. § 103(a) for obviousness over Tang et al. (WO 2001/57190). The Office states that "Tang et al teach administering the polypeptide of SEQ ID NO: 1401, which is 100% identical to SEQ ID NO: 4 of the instant invention...[for] treating Huntington's chorea...It is noted that although Tang does teach numerous polypeptides to be administered to treat numerous disease states, administration of Tang's polypeptides to Huntington patients is readily suggested by Tang, which therefore, is obvious to try based upon the specific suggestions of Tang" (Office action, pages 5-6). Applicants respectfully disagree.

The Office's obviousness rejection is based on the misconception that Tang et al. disclose treatment of Huntington's disease by administering SEQ ID NO: 1401. Applicants argued against this misconception in the previous response by reference to *Impax Labs. Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312 (Fed. Cir. 2008), and clearly demonstrated why the fact pattern of the present case is consistent with the fact pattern in *Impax Labs. Inc. v. Aventis Pharms. Inc.* (Response filed December 15, 2011, pages 12-14). The Office has completely ignored the arguments presented by Applicants and has merely changed the novelty objection into an obviousness rejection as the current claims recite administration to the striatum –a feature not found in Tang et al. This does not change the fact that Tang et al. do not disclose treatment of Huntington's disease with the protein having SEQ ID NO: 1401.

Given the speculative and tentative disclosure of Tang et al., the reference does not sufficiently direct or instruct a skilled artisan (*Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364 (Fed. Cir. 2011)). The Office's reliance on Tang et al. as the primary reference is also erroneous given that another more relevant primary reference exists.

Below, Applicants address that present invention is in fact novel and non-obvious over Tang et al. and solves a problem, which has not been recognized in Tang et al., namely the identification of secreted growth factors with expression in the nervous system for treatment of neurological indications associated with reduction or loss of neuronal function. In addition, Applicants demonstrate that the most pertinent prior art teaches away from the claims of the

present invention and that the use of NsG33 to treat Huntington's disease results in more than predictable results.

Problem solved by the present invention

The present invention aims at finding therapeutic utility in various neurological indications associated with reduction or loss of neuronal function for secreted growth factors with expression in the nervous system (see, for example, page 2, lines 4-5 of the specification as filed). Tang et al. provide no suggestions to solve this problem, as Tang et al. do not identify any proteins with expression in the nervous system and provide no hint that a particular group of genes have utilities that are specific to the nervous system.

According to Tang et al., each protein can be used to treat each and every disorder:

> "The methods of the invention also provide methods for treatment which involve the administration of the polynucleotides and polypeptides of the invention to individuals exhibiting symptoms or tendencies" (page 5, line 34 to page 6, line 1).

The person of skill in the art knows that this is not possible and will generally accept that the medical utility of a protein is restricted to one disorder or a group of related disorders involving the same mechanism.

Tang et al. do not qualify as a primary reference

Tang et al. disclose 1980 polypeptides (claim 20) and lists more than 20 pages of possible utilities (pages 40-60) which apply equally well to antibodies against the polypeptides and antisense polynucleotides which would down-regulate the expression of the polypeptides. Given these facts, it would have constituted several research projects to identify the biological activities and utilities of the proteins, antibodies, and anti-sense molecules of Tang et al.

If the Office's contention were correct that is was obvious to administer SEQ ID NO: 1401 of Tang et al. to the striatum to treat Huntington's disease, then it would be equally obvious to

administer all of the identified proteins, antibodies, and anti-sense molecules to the striatum and each and every tissue of the human body with the aim of treating each and every disorder listed in Tang et al.

The allegation that Tang et al. render obvious the treatment of Huntington's disease with SEQ ID NO: 1401 is based on hindsight knowledge only obtained with the present invention. It is just as obvious to use SEQ ID NO: 1401 for all the other disclosed potential uses. Tang et al. provide nothing more than the mere teaching that SEQ ID NO: 1401 is a human polypeptide sequence. Therefore, the disclosure of Tang et al. is equivalent to the disclosures provided by a database of human genes, such as the NCBI.

The Tang et al. reference can never be used as a primary reference against a later application claiming a specific utility of one of the numerous genes/proteins disclosed in Tang et al. (or in a database). A disclosure of this type cannot serve as a starting point for a person of skill in the art seeking to find the medical utility of a human gene or protein. According to the M.P.E.P. § 2145, a conclusion of obviousness requires that the reference(s) relied upon be enabling in that it put the public in possession of the claimed invention. Tang et al. provide sequences but no such enabling disclosure. Therefore, a conclusion of obviousness cannot be legally based on Tang et al.

Legal standard for obvious to try

According to the M.P.E.P. § 2145(X)(B), the "obvious to try" test only applies "where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success." Given the fact that Tang et al. teach approximately 2000 human genes and proteins, antibodies and silencing RNAs, and more than 20 pages of speculative, unsupported uses, the person of skill in the art is not faced with choosing from a finite number of identified solutions. The number is vast. The solutions cannot be said to be predictable or achievable with a reasonable expectation of success given the complete lack of information about specific utilities of the individual proteins of Tang et al. Therefore, it was not obvious to try administration of SEQ ID NO: 1401 to treat Huntington's disease.

Selection of the appropriate primary reference

In examining obviousness the complete prior art must be taken into consideration. The person of skill in the art would not only be aware of the teachings of Tang et al., but would also be aware of Fransen et al. (WO 2001/39786), which Applicants have previously cited. Fransen et al. concerns SMAF-1 and SMAF-2. SMAF-2 is identical to NsG33, and SMAF-1 is identical to NsG34, which is identified in the current application as being structurally related to NsG33 (Figure 5 of the present application). In contrast to the speculative and unsupported teachings of Tang et al., Fransen et al. provide specific information regarding SMAF-2 and SMAF-1.

Fransen et al. identify SMAF-1 and SMAF-2 as related proteins (Figure 1). In Example 1, the authors state that they identified an expressed sequence tag (EST) with a sequence related to SMAF-1 sequence. From this EST, the SMAF-2 coding sequence was obtained. Biological data and possible utilities concerning SMAF-1 have previously been provided by Fransen et al. in WO 1993/22437 (submitted in IDS dated January, 11, 2007). The utilities include use as anti-tumour agents, anti-inflammatory agents, growth activating compounds of T- and B-cells, bone repair compounds, inducers of immunosuppressive cells, inhibitors of anti-CSF or trypanocidal agents.

Fransen et al. provide data on isolation of a human and mouse SMAF-2 coding region (Examples 1 and 2), generation of a SMAF-2 knockout mouse (Example 3), expression of the protein in *E. coli* and mammalian cells (Examples 5 and 6), chromosomal mapping of the encoding gene (Example 4), expression and purification of His-tagged SMAF-2 (Example 7), generation of antibodies against SMAF-2 (Example 8), and expression analysis (Example 9). In addition, Fransen et al., at Example 10, provide data on SMAF-1 tested in various cytokines assays. From this example the authors conclude that both SMAF-1 and SMAF-2 specifically modulate the production of Th1, Th2, and/or Th3 cytokines (page 5, lines 8-10). Apparently, the function of SMAF-2 was inferred from its homology to SMAF-1.

Based on the biological data obtained with SMAF-1, Fransen et al. suggest use of the two proteins/genes in the treatment of "inflammatory bowel disease, leishmaniasis, trypanosomiasis,

malaria, schistosomatosis, HIV-associated diseases, measles, influenza, Candida-infection, tuberculosis, lepra, Borrelia-infection, Listeria-infection, Bordetella-infection, and Chamydial infection, allergies, psoriasis, multiple sclerosis, rheumatoid arthritis, transplant rejections, graft-versus-host disease, malignancies and diseases involving mucosal immunity" (page 11, lines 17-27). Malignancies are defined as including tumors and neoplasia.

Given that Fransen et al. constitutes a more specific disclosure than Tang et al. and contains disclosure that is specific to SMAF-1 and SMAF-2, the person of skill in the art seeking to find new medical utilities for NsG33 would consult Fransen et al. instead of consulting Tang et al. If for some reason, the skilled person would start with Tang et al. with the aim of identifying a therapeutic utility of SEQ ID NO: 1401, then that person would start performing a sequence similarity search and identify Fransen et al., which has specific information about the expression pattern of SMAF-2 and specific information about the therapeutic utilities of SMAF-1.

Applicants submit that the skilled person would not be motivated to test SMAF-2 in a model of Huntington's disease or an *in vitro* assay with striatal neurons given the therapeutic utilities predicted by Fransen et al. Fransen et al. teach away from any utility in the nervous system by suggesting that the utility of SMAF-2 lies, specifically, in modulation of cytokines.

Surprising results

As previously documented, NsG33 can be used to treat Huntington's disease and this has been demonstrated by the assignee in Jørgensen et al. (*Neurobiol. of Disease*. 41: 160-168, 2010; submitted in IDS dated February 18, 2011). Further *in vivo* data concerning striatal delivery of NsG33 can be found in Exhibit A (Jørgensen et al. *J. Mol. Neurosci.* 39: 104-116, 2009; submitted to the Office on Dec 23, 2009).

Two observations demonstrate more than predictable results. First, it is observed in Exhibit A that insterstriatal injection of NsG33/Meteorin protein "showed a widespread distribution of METRN (NsG33) throughout the injected striatum and overlying cortex" (page 10, left column).

It is concluded that "METRN readily diffuses and covers the entire striatum within a few hours. Compared to the GDNF family members (Hamilton et al., 2001), METRN diffusion is more efficient, which may be due to the lack of heparin-binding sites" (page 12, left column bottom to right column top). This means that it is easier to cover the whole striatum when administering NsG33 than when administering known growth factors with therapeutic potential in Huntington's disease, such as the GDNF family growth factors.

Second, it is observed in Jørgensen et al. that "secreted CNTF causes additional gliosis and upregulation of its own endogenous expression. This phenomenon is not evident with METRN" (Figure 3C, figure legend). In the discussion section it is concluded that "Meteorin was equally effective as the more well-characterised CNTF" (page 7, right column, lines 6-7 from bottom). Jørgensen et al. make the following conclusions:

> "Another notable difference between these two molecules is that while CNTF stimulates cell proliferation this has not been the case with Meteorin in multiple *in vitro* systems (Nishino et al, 2004). Therefore, Meteorin may be able to activate glia in the adult brain *without inducing cell proliferation*. Activation of glia is an important hallmark as these cells release neuroprotective factors and are capable of breaking down neurotoxic metabolites thereby helping neurons to survive in the injured of diseased brain (Sofroniew and Vinters, 2010)" (page 8, left column, middle) (Emphasis added).

Thus, NsG33 yields as good results as CNTF with respect to behaviour and protection of striatal neurons. In addition, the therapeutic use of NsG33 to treat disorders of the striatum is associated with more than predictable results in at least two respects. First, NsG33 does not induce cell proliferation in the brain but activates glia. This represents an unpredictable result over the use of CNFT. Induction of cell proliferation in the brain should be avoided as uncontrolled cell proliferation in the brain could lead to neoplasm or cancer. A protein that merely activates glia provides a more controllable therapeutic effect. Second, NsG33 diffuses readily in the striatum, which makes delivery easier and less susceptible to minor errors in delivery. This is an

unpredictable advantage over the use of GDNF family members, which are known to diffuse poorly in the brain because of heparin binding.

In conclusion, Applicants have demonstrated that the invention is not obvious in view of Tang et al. because of that reference's lack of disclosure, that Fransen et al. teach away from the current invention, and that the claimed methods provide more than predictable results over the prior art. Accordingly, the rejections should be withdrawn.

CONCLUSION

In view of the above Amendments and Remarks, Applicants believe the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 03-2095, under Order No. 50721-006002 from which the undersigned is authorized to draw.

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Respectfully submitted,

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